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Spontaneous abortion of unknown etiology

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Abortion has in the past come to have a variable meaning, so a declaration of the meaning of the writer is in order. In this paper abortion refers to an interuption of pregnancy and expulsion of the products of conception before the twenty-eighth week. However, in the interest of accuracy,, when the work of various men is discussed the terms they used will often be employed.

It is fair to ask--is there any indication for a discussion of spontaneous abortion? On the basis of various statistics, routine case histories and obstetrical histories which are apparently accurate, Taussig (1936) estimates that there are in the United States each year about 681,600 abortions, of which there are a maximum of 10,000 maternal deaths. The number of spontaneous abortions runs from twenty-eight percent to fifty-eight percent in various series of reports. This would mean from his previous estimate of the number of abortions a year, that from approximately 191,00 to 395,000 spontaneous abortions occur in the United States per year.

Bishop (1937) reports a series of 2,687 pregnancies in which the incidence of repeated spontaneous abortion of unknown etiology was 0.41 percent. Huntington (1929)

in a series of 104 consecutive abortions in private practice found eighty-two without known etiology. C. H. Peckham (1936) found that in a series of 2,287 abortions of all types [including therapeutic] 39.08 percent had had one or more previous abortions. Omitting the therapeutic abortions, there were 38.15 percent spontaneous abortions.

Vignes (1929) gives a long theoretical discussion of the cause of abortion. He considers the possibility of delayed menstruation [two days to over a week] being early abortions, and suggests the possibility of reabsorption of these embryos.

One general type of spontaneous abortion has etiology of an acute or traumatic nature. An example is operative trauma such as occurs in lower abdominal surgery during pregnancy, and which may lead to abortion. Physical trauma as experienced in automobile accidents or otherwise, may also cause expulsion of the fetus. Here, also, is considered sexual intercourse. Menge (1900) gives as evidence of the relationship between coitus and abortion, the fact that in many instances habitual abortion may be overcome only by the strict prohibition of sexual relations during pregnancy.

Occasionally heat or cold may be a direct exciting cause of the abortion, as it is well known that extremes of temperatures applied over the lower abdomen will stimulate the uterine musculature to contraction.

Stroke of lightning and powerful electrical shock will produce abortion. Severe psychic trauma will cause similiar results. Bouvocque stated that after the explosion of a powder mill in Grenelle he was called to see ninety-two women either aborting or threatened with abortion.

Irridiation of the pregnant uterus has proved to have such a uniformily destructive effect upon the developing ovum that it has been recommended as a non-operative means for therapeutic abortion.

Those causes of spontaneous abortion thus far mentiones are of an acute nature, and further, are not likely to occur repeatedly. The treatment is, obviously, the same as is used in any threatened abortion.

Thyphoid fever, cholera, scarlet fever, smallpox, erysipelas, encephalitis lethargica, and malaria produce abortion in about one-half of the pregnancies associated with these diseases. Of special danger to

the pregnant mother is croupous pneumonia, and the severer type of influenza pneumonia as reported in the epidemic of 1918.

Brucella Abortis has been claimed by some to cause abortion in women tending animals infected with this organism. Cornell and De Young (1929) found agglutinins in the placental blood of one patient who aborted, but in twenty-two others this test was negative.

Focal infection, while not a common cause of abortion, would seem to be a factor in certain women having a tendency to repeated spontaneous abortion of the ovisac. Curtis (1925) was one of the first to call attention to focal infection as an etiological factor. Reith (1927) experimentally used cultures of streptococci obtained from the tonsils and placenta of a woman who had had five spontaneous abortions. He injected these into four prengant rabbits and all four aborted; while of the ten pregnant rabbits in whom injections were made from cultures of other organisms, none aborted.

While syphilis is undeniably the most important factor in the premature expulsion of a macerated fetus in the last three months of pregnancy, it is only in exceptional cases the cause of abortion in the first

three months. It cannot, however, be denied that so insiduous an infection as syphilis may have a harmful effect upon the germinal cells of the parents, and thus indirectly have an unfavorable effect upon the development of the impregnated ovum. At the University of Minnesota Clinic, Adair (1935) found that the percentage of abortions in luetic women was not any greater than in women who did not have such infection. The work of Mc Cord (1934) among the colored population of the south would tend to indicate that in this race syphilis assumes a malignant form and is probably productive of abortion earlier in pregnancy and in a larger number of cases.

External factors also exist, which, if associated with relatively minor disturbances present in the mother, will result in fetal death and thus eventually lead to abortion. For instance, carbon dioxide, chloroform, phosphorus, and mercury are chemicals which may be transfered through the placenta and so give fetal death. The toxins of diphtheria and tetanus may act similiarly. Hyperpyrexia may at times have a like lethal effect.

Multiple pregnancy is a frequent factor in premature labor and at times may lead to late abortion. This is

more apt to occur if there is an excess of amniotic fluid, or if there are three or more fetuses.

Litzenberg (1932) believes that a vast majority of abortions can be traced to abnormalities of the endometrium, decidua, and placenta. Placenta previa, although, more often responsible for interruption of pregnancy after the period of viability, does occasionally give rise to abortion between the third and sixth month. Rhentner and Pigeaud (1927) state that in abortion of three to five month gestation, placenta previa is the cause in fifteen percent of the cases.

A twist of the umbilical cord has often been blamed for fetal death and the resulting abortion. A careful check-up will usually disclose, however, that the twist of the cord occured after the death of the fetus.

The suggestion was made by Aschner that some cases of habitual abortion are due to primary diseases of the placenta, some of which cases heretofore classified as toxic nephritis, should be explained as toxic albuminuria of placental origin.

In cases of hydatid mole pregnancy does not usually proceed beyond the third month. Deciduitis may give abortion.

Lacerations of childbirth sometimes cause abortions, particularly if the pelvic floor is destroyed or if they

extend into the parametrium on either side of the cervix.

Retroversion of the uterus is commonly blamed for abortion, but this is justified in only a small percentage of cases. Since retroversion occurs in about one-fourth of all women who have had children, and since, with but few exceptions, during pregnancy such a retroverted uterus will spontaneously correct itself, this etiological factor should not be stressed. Incarcirated uterus is, of course, excepted.

Large fibroids, by cutting off the blood supply to the maternal sinuses, may cause abortion.

Urinary fistula, bladder calculi, urethral or bladder colic, intestinal conditions, liver and gall-bladder disease, and diabetes are all recognized as conditions which may percipitate expulsion of the non-viable fetus.

That the nutrition of the mother must play an important part in the development of the ovum and hence be responsible at times for abortion is self-evident.

Old age with accompanying arterio-sclerosis and hypertension may be satisfactory explanations of abortions in certain cases.

A careful check of the abstetrical patient with a history of previous spontaneous abortion may reveal one of the above chronic or infectious conditions.

If this be so, then the immediate care should be directed at removal or treatment of that factor.

The third group, those of obscure or unknown etiology, presents an interesting study.

Of human abortion ova dating from the first month, Mall (1921) found only a fifth normal, and from the second month only a half normal. Huntington (1929) in a series of one hundred and four consecutive abortions in private practice found eighty-two where there was no known pathological cause. Because the products of conception presented abnormal development, an etiology of "defective germ plasm" was established by gross and microscopic inspection by a pathologist. Uterine displacements, slight endometritis, chronic nephritis and low basal metabolic rates were considered as adequate explanation of the other group of twenty-two. He says without qualification that defective germ plasm is the cause of most spontaneous abortions, this condition being caused by over or under nourishment, focal infection, faulty endocrine function [particularly hypothyroidism], defective development of the corpus luteum and anterior pituitary hormones. He also mentions that spermatazoa may have a faulty germ plasm which causes abortion. Streeter (1931) concurs in this opinion.

Riddle (1927) attributes the higher abortion rate in males to the greater vitamine and metabolic requirements in that sex.

Mayer (1933) believes that such an ovum with diminished vitality may lack the necessary aggressiveness to embed itself into the uterus.

G. L. Moench made careful histological studies of pathological spermatozoa and found that wives of individuals having a high percentage of such sex cells are apt to show greater than average frequency of abortion.

Of unusual interest are the two cases of repeated abortion with blighted ova reported by Saunders (1927), in which no reason could be found in the wife. The husband showed definate pus in the semen due to non-venereal prostatitis. After massage treatment the pus disappeared and the next conception, a few months later, was carried to term in both cases.

Paroli (1928) studied a series of twenty-seven cases of spontaneous abortion in which lues and other factors could be excluded and found that twenty-six of the twenty-seven pairs of parents belonged to different blood groups. Tranquilli-Leali (1932) also believes that such constitutional dis-harmony between mother and

father may be a cause for abortion. He studied fourty-one habitual abortions without explainable cause and found in thirty-eight incompatibility of blood groups of husband and wife, and only three pairs with the same blood group.

Taussig (1936) states that insufficiencies of the secretion from the anterior pituitary gland are indirectly responsible for some cases of abortion through arrested development of the uterus. In such women pregnancy does not readily take place, and when it does, the relatively small size of the uterus leads to a tendency to abortion. Weinzerl (1933) cites six cases of habitual abortion in women between twenty-four and thirty-three who had such a hypoplastic condition of the uterus.

In every case giving a history of previous spontaneous abortion the basal metabolic rate should be determined before the next conception and repeated during the early months of pregnancy. Abruzzese (1929) found foulty functioning of the thyroid in sixteen of thirty women who had had an abortion without physical cause. In his sixteen cases, a basal metabolism test showed five times that it was too low, and eleven times that it was too high. Huntington (1925) mentions a

defidient thyroid secretion as responsible for cases of abortion. Mayer (1933) calls attention to the fact that experimental injection of thyroid extract tends to shorten pregnancy while a thyroidectomy tends to prolong it. He advises giving iodine in cases of habitual abortion due to hyperthyroid secretion. Kane (1936) evidently accepts the role of the thyroid in abortion, because in his series of cases to be mentioned later, extract of thyroid was used routinely.

In the valley of the Lillooet River near Vancouver, it is recognized that without the prenatal feeding of iodine to pregnant stock during the winter months, eighty to ninety percent of the calves and foals die at birth. Kemp (1933) mentions this and goes on to analyse 19,730 deliveries in Vancouver from 1925 to 1929 inclusive. He found that in the three hundred and thirty idiopathic stillbirths, the incidence in mothers not treated with pre-natal iodine was six and one-third times as great as in those who were so treated. Further, there were in Vancouver General Hospital from 1930 to 1932 inclusive 4,813 deliveries. Of these, seven hundred and fourty-one mothers who had pre-natal iodine had no idiopathic stillbirths, but of the 4,073 who had no pre-natal iodine there were fifty idiopathic

stillbirths.

Le Lorier and M. Mayer (1935) report a case who had six repeated spontaneous abortions. They administered thyroid preparations during the seventh pregnancy and were successful in the spontaneous delivery of a normal child. The woman became pregnant again while still lactating--attributing the amenorrhea to that fact. As a result she was not on thyroid therapy and again aborted.

Huntington also mentions a patient in which the basal metabolic rate was normal, but had aborted. In a later pregnancy she was carried to term on five to ten grains of thyroid extract daily. It is difficult to account for or interpret this phenomenon.

In 1913 Seitz suggested careful observation of the corpus luteum whenever possible for pathological changes in cases of habitual abortion. Walter Long Williams in his chapter "Abortion in Animals" in Taussig's latest monograph on abortion mentions that digital expulsion of the corpus luteum from the ovaries of pregnant cows will always result in abortion. What, then, is the physiology of the corpus luteum which may indicate its role in pregnancy?

That the corpus luteum produces simultaneously

in addition to oestrin, another hormone, which has as inhibitory effect on ovulation and a sensitizing influence on the endometrium, was first suggested by the experiments of Leo Loeb (1907). This investigator found deciduoma formation /progestational reaction/ in the endometrium of the rabbit nine days after sterile coitus--the fallopian tubes having been tied off prior to coition. When he destroyed the corpora lutea by means of a cautery, deciduoma formation was not in evidence; in fact, the next oestrus appeared prematurely.

Bouin and Ancel (1910) corraborated the findings of Loeb that the corpus luteum prepares the uterine mucosa for implantation and nourishment of the ovum, and that it is indispensable for the maintenance of early pregnancy.

Weichert in 1928 advanced knowledge of the function of the corpus luteum by the following experiments:

1--He inhibited ovulation in the normal rat by a series of injections of an aqueous extract of corpora lutea prepared by the method of Hisaw (1928). This result corraborated that previously secured by Papanicolaou (1926) in the guinnea-pig.

2--By injection of the lutein hormone, progestin, he produced in the isolated rat with normal oestrous cycles, an exaggerated progestational endometrium /placentomata/.

3--Injections of the lutein hormone, progestin, in castrated rats produced no noticeable effect in the lower genital tract. If, however, such animals were first brought into artificial oestrus by treatment with oestrin, and then treated with luteal extract, placentomata were formed.

4--The castrated guinnea-pig, which normally has a thirteen day cycle, developed no progestational endometrium if eastrated three days after oestrum. However, when the lutein hormone was injected four days after castration, the formation of placentomata did take place.

Corner and Allen (1929) corroberated those findings and further established without a doubt the dependence of the endometrium on the corpus luteum for the production of progestational changes and for the maintenance of pregnancy. They spayed rabbits twenty-four hours after mating, at which time the fertilized ova had already been in the tubes five to ten hours.

Typical endometrial changes did not occur. They were, nevertheless, brought about and maintained by injections of corpus luteum hormone, progestin.

Frank (1929) showed corpus luteum essential to the pregnant rabbit for at least the first nine days. In subsequent experiments Corner and Allen were able to produce placentomata in castrated rabbits by injections of oestrin and progestin. Brouha (1927) confirmed these observations. Clauberg (1930) produced similiar results in the castrated mouse.

Corner suggested the name "progestin" for the extract of corpus luteum which he personally prepared.

In 1926 Papanicoloau preformed experiments which attested the internal secretory function of the corpus luteum. He reported suppression of ovulation and oestrus in the guinnea-pig caused by injections of an aqueous extract of corpus luteum.

Macht (1930) and Imparato (1928) confirmed this and likewise observed that daily injections of one cubic centimeter of aqueous solution of corpus luteum produced a distinct inhibition of the oestrous cycle in the guinnea-pig, sometimes for seventy or more days. When injections were discontinued, the normal cycle was re-established.

Gley (1928), Winter (1930) and others similiarly demonstrated inhibition of follicle maturation in the rat and mouse, by injections of aqueous solutions of corpora lutea.

Hisaw (1930) first demonstrated inhibition of uterine contractions by progestin. Morrell demonstrated the ability of progestin to counter-act and nullify the effect of pituitrin on the exparpated guinnea-pig uterus.

Miklos (1930) was able to prolong pregnancy in the rat not only beyond the normal, average length, but even beyond the longest term, by injections of aqueous solutions of corpora lutea. In some of the animals thus treated, and in which pregnancy was thus prolonged, the young were born dead.

Smith and Smith (1931) have shown that injections of large doses of oestrin in normal and spayed female rabbits results in only ten percent of the dose being excreted. If, however, progestin is simultaneously administered, the amount of oestrin excreted is from five to seven times as great as when this is not used. So it is suggested that progestin promotes excretion of oestrin and thus regulates the balance.

Hisaw described the physical and chemical

properties of progestin as follows:

1--It is fairly stable, being destroyed at 50 degrees C.

2--It is stable in weak acid solutions, in aqueous, or neutral alcoholic colutions.

3--It is destroyed by alkaline solutions.

4--It is most soluble in water, and moderately soluble in acidified absolute alcohol.

5--It is insoluble in lipoid solvents.

6--It readily passes through a Berkefeld filter; so sterile aqueous solutions can easily be prepared.

7--It passes through ultra-filters and dialyzes slowly through collodion bags previously tested with Congo red.

Progestin can be prepared in the following manner:

1--Grind a mass of corpora lutea with sand and extract with acid alcohol for twenty-four hours. This extracts the oestrin and progestin.

2--Under reduced pressure at a temperature below fifty degrees C. evaporate to an aqueous sludge.

3--Neutralize and extract the oestrin by repeated washings with ether.

4--Dialyze for twenty-four hours through a collodion bag first tested with Congo red.

5--Evaporate as in #2. A clear yellow solution remains--it contains the progestin and also a certain small portion of oestrin, not enough to have a marked influence.

The various qualitative tests devised to test for progestin are:

1--Papanecolaou's based on suppression of ovulation and oestrus in the guinnea-pig.

2--Weichert's which is the production of placentomata in castrated animals brought into artificial oestrus.

3--Hisaw's in which virgin adult guinnea-pigs are injected at the time of full oestrus, and twelve hours later the pubic ligament becomes loose.

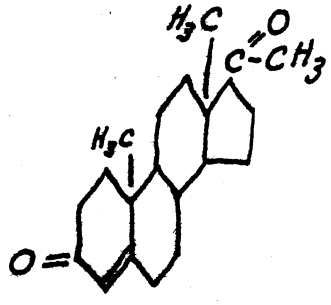
4--That of Dr. J. A. Morrell which is employed in the Research and Biological Laboratories of Squibb and Sons: The extirpated uterus of a guinnea-pig is suspended in Ringer's solution and corpus luteul axtract added. After a few minutes ordinary posterior pituitary hormone is added. In the presence of active corpus luteum hormone, the usual contractile effect of the

posterior pituitary principle is abolished. Corner and Allen devised a quantitative test for this hormone--called the Rabbit Unit. A doe is mated and after 18 hours is subjected to removal of both ovaries and a portion of one of the uterine horns, about one centimeter in length. Ordinarily this proceedure immediately checks endometrial and embryonal development. The test animal is then given five daily injections of the luteal extract--which tends to promote endometrial and embryonal growth despite removal of the corpora lutea. On the sixth day the animal is killed, the embryos, if present, examined and removed, and the uterus submitted to microscopic examination and comparrison made with the cornual tissue previously removed at the time of castration. The minimum amount of progestin which when divided into five daily doses and injected into a recently mated, castrated doe weighing 3-4 Kg., will alter the endometrium to a state similiar to that of the eighth day of normal pregnancy is called a "rabbit unit".

Another measure of the potency of progestin is the Clauberg unit which is roughly equal to one-half a Corner-Allen unit. The Standardization Committee of the League of Nations has adopted an International

Standard of Potency defined as the progestational activity present in one mg. crystalline corpus luteum hormone (1935). It is approximately equal to one Corner-Allen unit. The quantitative test now in general use, and recognized (May,1936) by the Council on Nomenclature of Endocrine Principles [The American Medical Association] is that of Corner and Allen.

The same group also credit complete determination of the structural formula and earliest method of artificial preparation to Butenandt, who in 1934 showed the structure to be:



They recognize the following as correct terminology:

Progesterone to designate the pure chemical substance of the above structure.

Progestin as a general term to indicate the substance [and other chemically allied substances having similiar action in case any such substances are subsequently discovered] without reference to the state of purity.

Allen, Butenandt, Corner and Slotta use the following terms as indicated in a letter of agreement (1935):

α-Progesterone is that one of the two different chemically pure forms which melts at 128 degrees [uncorr.].

β-Progesterone is that one of the two different chemically pure products which melts at 121 degrees [uncorr.].

Since then additional experimental work has been done with the corpus luteum hormone, part of it on the human female. Lubin and Clark (1936) have successfully used progestin in the treatment of after-pains in a large group of cases and got ninety percent relief.

Rowland and Mc Phail (1936) showed that progestin caused the uterine glands to elongate, become twisted, and the mouths of these glands to become open.

Watson (1936) reports a case in which the woman had intact ovaries, but symptoms of ovarian hypofunction. Oesterone and progesterone were given in massive doses for three days, and on the fourth the uterus was removed and examined histologically. He concludes that one or both of these hormones, of the combination, causes extensive endometrial growth and development in the human.

Lloyd (1937) on experimental evidence gained

working with rabbits concluded that progesterone has as its initial effect the stimulation of cell-division in the uterine epithelium. His conclusion is based on the initial appearance of mitotic figures in great excess in those castrated animals where progesterone was injected, over similiar animals where oestrin was used.

Hisaw and Greep (1936) showed that in the monkey synthetic progesterone has the same effect as corpus luteum extract. Robson (1936) demonstrated that the effect of progesterone can be nullified by 1/75 of its weight of oesterone if injected simultaneously.

Bloch (1936) demonstrated progestin in sows blood and showed that less than one R. U. of progestin could be extracted from eight liters of sows blood extracted with benzene, and less than one R. U. in twelve liters extracted with methyl alcohol. He also concludes that the total volume of circulating blood in the rabbit contains less than one R. U. Using up to 500 cubic centimeters of blood of pregnant women negative results were obtained.

Pratt and his group (1936) found that it requires fourty human corpora lutea to obtain one Clauberg unit. Sixty to one hundred grams of fresh corpora lutea in

all cases gave positive tests. McGinty, Mc Cullough, and Wolter (1936) showed that the human placenta contains seven Clauberg units of progestational hormone /progestin/ per kilo of tissue, and that significant progestational effects are seen with but fifty grams of fresh human placenta.

Fall, Lackner and Krohn (1936) studied the inhibiting effect of progestin in the human being by use of the method of Moir. This consists of introducing under sterile precautions a hydrostatic bag into the uterus of a seventh day parturient patient. They concluded in part:

1--One rabbit unit /Corner/ of the lutein hormone progestin completely nullifies the effect of one cubic centimeter of solution of anterior pituitary, whether given before or after the response to the injection of the solution of pituitary.

2--One rabbit unit of progestin inhibits human uterine contractions in a seventh day parturient woman.

3--The hypodermic injection of ¼ grain of morphine sulphate not only failed to diminish contractions of the human puerperal uterus produced by injection of one cubic centimeter of solution

of pituitary, but actually seemed to augment them.

Reynolds and Allen (1937) found that progesterone has the property of reducing myometrial tonicity. Krohn, Lackner and Saskin (1937) proved that progestin decreased the motility of the normal non-pregnant and non-puerperal uterus /for at least two hours (1935)/. Also that it decreased the motility and stopped the bleeding in a woman suffering from functional menarrhagia.

There is, then, a very close relationship between progestin and the endometrium and myometrium. What may be the role of this hormone in spontaneous abortion? If there is a deficiency of progestin the mechanism of abortion may be:

1--Relative increase in oesterone, and actual increase due to decreased elimination, which sensitizes the uterus to pituitrin, thus initiating contractions.

2--Inadequate decidual reaction resulting in:

a--Undernourishment and death of the fertilized ovum with expulsion or reabsorption.

b--Deficient placentation with a resulting deficiency of progestin in the placenta.

3--Increasing hemorrhagic tendency of the endometrium may produce premature placental detachment.

With the forgoing as a basis, what has been the clinical experience with progestin in the treatment of spontaneous abortion? Hirst in 1918 treated habitual abortion with the aqueous extract of cattle lutea as injeactions. He reports two cases in which live babies were born and one which aborted, and also mentions that Dannreuther successfully treated one case /Graves Gynecology/ by oral administration of corpus luteum extract.

Hannes in 1919 suggested that such an extract might be useful in the treatment of spontaneous abortion. In 1920 Hofbauer noted an inhibition of uterine contractinns following the use of a preparation called ovoglandol in threatened and habitual abortions.

In 1921 J. Halban advised use of corpus luteum extract in abortion. Glismann (1928) reported about twenty cases of recurrent abortion successfully treated with a corpus luteum extract called "lipo-lutin". The products of the above men were not standardized and probably contained rather small amounts of the nidatory principle, yet the results were encouraging.

Antecki and Zwolinski (1928) reported twenty-one cases of habitual abortion, of which nineteen went to term with daily treatment of "lutophorin", a corpus

luteum preparation. H. Wolfsohn (1932) used "luteogan" with success in seven of ten cases of habitual abortion. He attributed one of the three failures to fibroid uterus, and another to hydadit mole. Weinzierl (1933) reported a series of six cases of habitual abortion successfully treated with luteal hormone, and Bracht in the same year reported a similiar series of four.

Wagner (1932) and Knab (1933) mention that they have used the corpus luteum hormone with success in the treatment of several cases of habitual abortion. There are also isolated case reports of similiar success by Lopez-Doriga, Lind, Patti, and Shea.

Sellheim (1933) used the blood serum of normal pregnant females in the treatment of five cases of habitual abortion and two cases of threatened abortion. He believes that the substance which prevented abortion in these patients was the corpus luteum hormone in the blood of the normal pregnant women.

G. J. Hall (1934) presents a case of habitual abortion treated with progestin with satisfactory results. F. B. Smith and R. Al Johnston (1935) believe there is a rational explanation for use of progesterone in all pregnancies where there is a history of one previous abortion. Kane in 1935 reported a series of twenty-six cases with four failures, but this series will be

mentioned again when it is included in his later and more complete series.

Krohn, Falls, and Lackner (1935) reported a series of nineteen patients. Of these fifteen had had one or more previous spontaneous abortions. Of these they reported failure in four cases, but one carried to eight months with fetal death twelve hours post-partum due to atelectasis, so perhaps this should also be called a success. One case had had a previous premature labor and was successfully carried through the pregnancy. The other three cases had had no history of previous abortions. Two of these were diagnosed threatened abortion at about three and one-half months; one was treated successfully and the other aborted at four months. The other of these last three was called threatened miscarriage at six months and was treated with success.

Their routine of treatment can be summarized thus. Habitual abortion patients recieved one cubic centimeter /one Rabbit U/ of progestin intramuscularly two times a week until the thirty-second week of gestation, and were permitted to be ambulatory if no symptoms of abortion were apparent. Threatened abortions were put to bed and recieved one Rabbit U twice daily until all

symptoms subsided, then one Rabbit U once a day for the next week, following which the habitual abortion routine was carried out.

The same men in 1936 reported a more complete series of cases including those above described. This last series can be summarized:

	Cases	Successes	Failures
Threatened abortion only	11	10	1
Habitual abortion only	13	10	3
Threatened and habitual abortion	17	14	3
Total cases treated with progestin	41	34	7

They state that the source of their original hormone was discontinued and so the remainder of the cases were treated with a product of which 1/25 to one Clauberg unit was used, according to the severity of the symptoms.

These men conclude:

1--The use of progestin in habitual and threatened abortion is logical and valuable.

2--Thirty-four of fourty-one cases of threatened and habitual abortion were successfully treated with the corpus luteum hormone.

3--All babies delivered in the successfully treated cases were normal. In two of the cases that aborted the fetuses were abnormal.

Kane (1936) defines habitual abortion as "Repeated spontaneous abortion which describes the condition

without admitting failure in diagnosis--by dismissing it as simply a habit." He states that the presence of sufficient progesterone is essential for nidation and growth of the fertilized ovum in the endometrium. Also that progesterone obtained from the corpus luteum extract contains oestrin /antagonistic to progesterone/ in varying amounts so that its effect in the patient is not predictable, and with the present availability of pure commercial progesterone failures in treatment should be eliminated. He reports his more complete series of fourty patients, all in private practice, and their abortion history was as follows:

20---one previous abortion
14---two previous abortions
4---three previous abortions
1---four previous abortions
1---six previous abortions
10---had borne one child, then aborted one to three times.

His routine of treatment was begun as soon as the patient presented herself and was as follows:

1--Prolutan 1/25 rat U given intramuscularly each other day for ten doses.

2--Then this routine repeated at three week intervals until the end of the fourth month.

3--One-half grain of dessicated thyroid three times a day for two weeks, four grains of Na I three

times a day for the next two weeks, alternating thus to the end of the sixth month.

In the first twenty-six cases of this series two cubic centimeters of corpus luteum was used instead of prolutan.

His results showed no failures in the fourteen cases treated with prolutan. As mentioned previously he had four failures in twenty-six cases treated with corpus luteum extract. He mentions that one patient aborted spontaneously in her first pregnancy, also in the second when treated with corpus luteum extract, but in the third was carried through successfully on prolutan. Of the children born to those carried through successfully, one had spina bifida, one was operated for congenital pyloric stenosis, and a third had imperforate anus, a congenital heart lesion, and Mongolism.

Bishop (1937) reported nineteen pregnancies in sixteen patients with habitual abortion history and had successful results in seven pregnancies, in six the pregnancy was advanced farther than ever before, and seven showed no change whatsoever. This series shows much different results than others treated with progestin or progesterone--which Bishop used. It may be said that there was evidently no routine treatment

used, and it further seems that no additional measures were instituted when abortion was eminent. There was also poor control as illustrated, for example, by the fact that one listed as a failure was operated in the twenty-second week--after recieving 42 Rabbit U of progestin from the twelvth to the eighteenth weeks--for strangulated ovarian cyst and on the next day aborted an hydatidiform mole. No further comment is needed on that series.

Clauberg (1937) recommends sorpus luteum extract in the treatment of habitual abortion. Gersherdeld (1937) reports a series of twenty-seven women with habitual abortion treated with progesterone. Of these twenty went to term or had a living baby earlier, and only seven aborted.

In 1922 Evans and Bishop showed that animals raised on a diet free of Vitamine E are chiefly sterile in the first generation and wholly so in the second. The ovarian functions are not disturbed--rather there is sub-placental extravasation of blood with ultimate reabsorption of the products of conception. Palmer and Kennedy (1923) confirmed this.

Evans and Bishop (1927) found that in rats, embryos of animals on E-free diet showed general under-development

most marked in the mesoderm. The embryos continue to be subnormal up to the time of death. The yolk-sac of E-free gestations is the seat of important abnormalities consisting in a marked reduction in size and number of entodermal villi and the mesodermal blood islands from the time of their appearance /tenth day/. Also that there is impairment in the outgrowth and full differentation of the allantois in later E-free gestations.

The maternal placenta of mothers on E-free diet, though smaller than normal and showing distended vessels in the dicidua subplacentalis, is not greatly altered structurally up to the time of fetal death. After fetal death the placenta continues to grow for several days in a nearly normal way, but the labyrinth is being absorbed due to the degeneration of fetal capillaries.

There are no important and constant changes observed in the embryo itself except in the mesenchyme. The hemopoetic organs are reduced. In some cases the entodermal anlage of the liver is subnormal, but this is not always the case. A striking reduction in the number of blood vessels present in the heart and vascular system of the embryo has also been observed.

They conclude that vitamine E is probably needed

in some obscure way by all the fetal tissues, but the middle germ layer and its products appear to be specially sensitive to its withdrawal, exhibiting marked alterations in its absence.

This worker also found that in the rat /period of gestation is eighteen days/ after establishing the minimal effective dose of wheat germ oil necessary to ensure the birth of living young, it was possible to show that the same total dose of this substance may be successfully administered as a single dose on or within five days after the beginning of gestation. This may be given either by mouth or intraperitoneally.

Vogt-Möller and Bay (1931) obtained favorable results in treatment of sterility in cows with wheat germ oil.

Sure (1933-1934) concluded that lack of fertility in animals on a milk diet was due to lack of some factor other than protein fat-soluble "A", the anti-rachitic vitamine, or the water soluble "B" vitamine. He corraborated the work of Evans and Bishop. He found that wheat germ oil, cotton seed oil, sorn oil, and palm oil are the only vegetable and fruit oils which he studied that permitted normal lactation and exhibited anti-sterility properties. Peach kernel,

soy bean, peanut and olive oils were effective in curing sterility. He found that reducing the concentration of wheat oil, corn oil, and cotton seed oils in the basal rations resulted in greater infant mortality.

Can this vitamine, then, be used successfully in treatment of abortion?

Vogt-Möller (1933-1934) treated twenty cases of habitual abortion with wheat germ oil and /or/ wheat germ. He had seventeen living children born. He suggests that due to varying physiological needs in different individuals, those cases successfully treated may have had a hypo-vitaminosis.

Juhász-Schäffers (1934) reported five patients having had two or more abortions /habitual/ treated with wheat germ oil. They all delivered living babies.

E. Shute (1936) found that the blood serum of rats on a vitamine E-free diet developed the ability to resist digestion by tryptic ferment. This resistance is exactly comparable to the blood serum of many aborting women. The administration of vitamine E quickly overcame this condition in both rats and human females. The change in rats is approximately co-incident with the state of vitamine E deficiency in the animal.

He found this property in the blood of seventy percent of aborting women. He reports fourty-six women with one or more previous abortions all treated with wheat germ oil. Of these, thirty-four delivered normal babies at or near term. Of nineteen threatened abortions, thirteen had the same results.

Watson and Tew (1936) report that they use vitamine E in the form of wheat germ oil in gelatine capsules containing one cubic centimeter each. They use three to six cubic centimeters per day by mouth--from as early in pregnancy as possible to well past the time abortion usually occurs and often until completion of pregnancy. If these patients become threatened abortions, the dosage is increased materially--to as much as twenty cubic centimeters a day--without ill effect.

In their series of eighteen women who had had three to fifteen spontaneous abortions, thirteen delivered normally with live babies. Seventeen women had had two previous spontaneous abortions, and of these twelve were successfully treated.

Currie (1936) reported a series of twenty-nine pregnancies in twenty-three patients all having had at least one previous abortion; only one patient having

had a single abortion of known etiology /albumenuria/, others having had similiar abortions plus one or more of unknown etiology. Seventeen of these patients had had repeated spontaneous abortions of unknown etiology.

He got twenty-tree living babies, one of which died due to a structural deformity of the throat. There was one abortion, and the other six were at that time past the sixth month of pregnancy. Unlimited wheat germ oil was given over a period of five months in all cases.

Danforth (1936) mentions the need of vitamine E for development of the ovum and during the period of lactation. Bishop (1937) in his poorly controled series mentions treating two patients, each having had three or more abortions before the fifth month. They were treated with vitamine E and one was carried through successfully, the other aborted.

Another endocrine product--emmenin, one of Collip's factors from placental extract--has also been used in the treatment of abortion. McGoogan (1938) reports that he used this preparation successfully in a woman's second pregnancy, the first having terminated in abortion. Her third pregnancy was untreated and likewise ended with abortion.

What, then, is the rational proceedure in attending a patient who presents herself for care during pregnancy and has a history of previous spontaneous abortion? The first step is to determine from her history if there was any acute proceedure or accident that clearly explains the previous abortion. If not, a careful physical examination and laboratory examinations may reveal one of the chronic conditions capable of being the exciting factor. Such a condition would then be treated as indicated.

If none of these causes can be found, then a seminal speciman from the husband may reveal pathological spermatozoa and that condition remedied. Failing this, it is logical to institute one of the hormonal or vitamine routines. That of Kane is a crafty combination of thyroid and progesterone. It may be suggested that wheat germ oil could even be given as a supplement to this.

It can be concluded that it is evidently possible to carry through pregnancy a large percentage of those women with a history of previous spontaneous abortion. It must be remembered, however, that from the cases herein reported, a relatively high number of fetal mal-developments must be expected when such women are taken through pregnancy under such regimes.

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